

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/023880

International filing date: 23 July 2004 (23.07.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/555,626
Filing date: 23 March 2004 (23.03.2004)

Date of receipt at the International Bureau: 23 August 2004 (23.08.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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APPLICATION NUMBER: 60/555,626

FILING DATE: *March 23, 2004*

RELATED PCT APPLICATION NUMBER: *PCT/US04/23880*

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13049 U.S. PTO

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PTO/SB/16 (08-03)

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

Express Mail Label No. EV14660353US

22264 U.S. PTO
60/555626



032304

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<input checked="" type="checkbox"/> Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
Processes for Preparing Substituted Phenylpyrazole Ureas and Intermediate Thereof					
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ENCLOSED APPLICATION PARTS (check all that apply)					
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<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76					
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Respectfully submitted,
SIGNATURE

Christine A. Goddard

[Page 1 of 2]

Date

03/24/04

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REGISTRATION NO.
(if appropriate)

46,731

Docket Number:

83.US1.PRO

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Docket Number 83.US1.PRO

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[Page 2 of 2]

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**PROCESSES FOR PREPARING SUBSTITUTED PHENYLPYRAZOLE UREAS
AND INTERMEDIATES THEREOF**

5

FIELD OF THE INVENTION

The present invention is directed to processes for the preparation of substituted phenylpyrazole ureas that are useful as 5-HT_{2A} serotonin receptor modulators for the treatment of disease.

10

BACKGROUND OF THE INVENTION

G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified.

15

20

Under physiological conditions, G protein-coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

25

A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

30

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to an anti-psychotic treatment, approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT₁ through 5-HT₇, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT₂ subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The human 5-HT_{2C} receptor was first isolated and cloned in 1987, and the human 5-HT_{2A} receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT_{2A} and 5-HT_{2C} receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

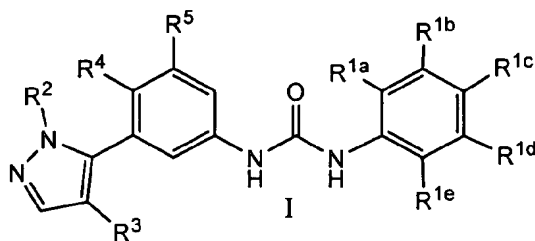
Isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{1C} receptor (now known as the 5-HT_{2C} receptor) and the entire human 5-HT_{2A} receptor are described in U.S. Pat. Nos. 4,985,352 and 5,661,012, respectively. Mutations of the endogenous forms of the rat 5-HT_{2A} and rat 5-HT_{2C} receptors have been reported to lead to constitutive activation of these receptors (5-HT_{2A}: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, 5-HT_{2C}: Herrick-Davis, K., and Teitler, M. (1996) *Society for Neuroscience Abstracts*, 22:699.18.; and Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138).

Small molecule modulators of serotonin receptors have been shown to have a variety of therapeutic applications such as for the treatment of any of the diseases listed above. Accordingly, there is an ongoing need for the preparation of compounds that can

modulate serotonin receptors. The processes and intermediates described are directed to this and other needs.

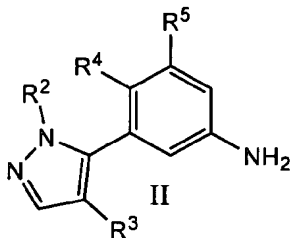
SUMMARY OF THE INVENTION

- 5 The present invention provides processes for preparing compounds of Formula I:

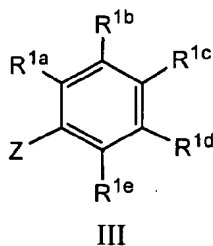


wherein constituent members are defined herein; comprising:

- a) reacting a compound of Formula II:

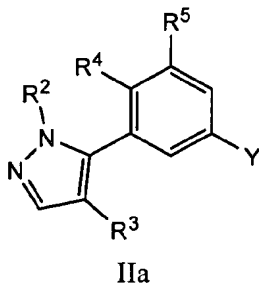


- 10 with a compound of Formula III:

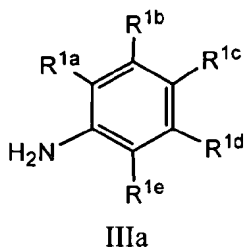


wherein Z is an isocyanate group (–NCO) or isocyanate equivalent, for a time and under conditions suitable for forming said compound of Formula I; or

- 15 b) reacting a compound of Formula II with an isocyanate-generating reagent for a time and under conditions suitable for forming a compound of Formula IIa:

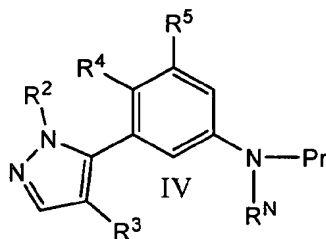


wherein Y is an isocyanate group or isocyanate equivalent; and reacting said compound of Formula IIa with a compound of Formula IIIa:



5 for a time and under conditions suitable for forming said compound of Formula I.

The present invention further provides a process for preparing a compound of Formula II comprising reacting a compound of Formula IV:



10 wherein:

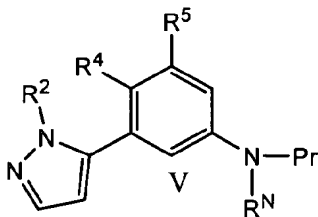
Pr is an amino protecting group; and

 R^N is H ;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group; with a deprotecting agent for a time and under conditions suitable

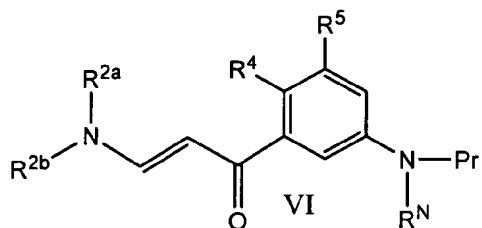
15 for forming said compound of Formula II.

The invention further provides processes for preparing compounds of Formula IV comprising reacting a compound of Formula V:



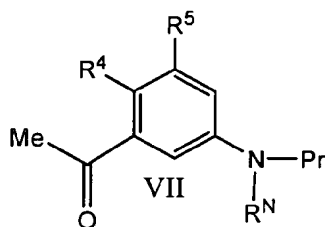
20 with a halogenating reagent for a time and under conditions suitable for forming said compound of Formula IV.

The present invention further provides processes for preparing a compounds of Formula V comprising reacting a compound of Formula VI:

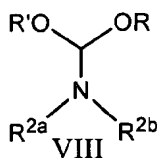


wherein R^{2a} and R^{2b} are each, independently, C_{1-4} alkyl, with an alkyldiazine having the formula NH_2NH-R^2 for a time and under conditions suitable for forming said compound of Formula V.

The present invention further provides a processes for preparing compounds of Formula VI comprising reacting a compound of Formula VII:

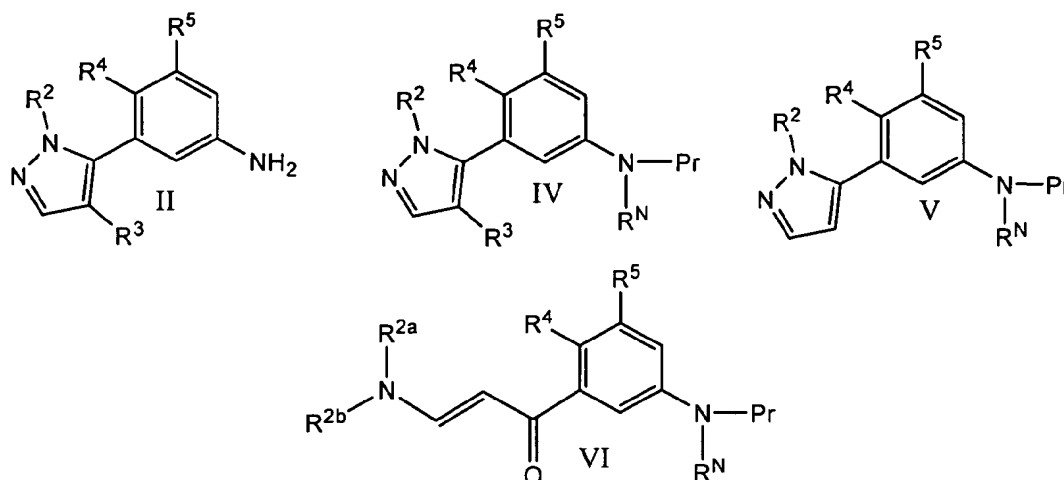


with an acetal of Formula VIII:



wherein R and R' are each, independently, C_{1-6} alkyl, arylalkyl or alkylaryl, or R and R' together with the O atoms to which they are attached and the intervening CH group form a 5- or 6-membered heterocycloalkyl group, for a time and under conditions suitable for forming said compound of Formula VI.

The present invention further provides process intermediates of Formulas II, IV, V and VI:



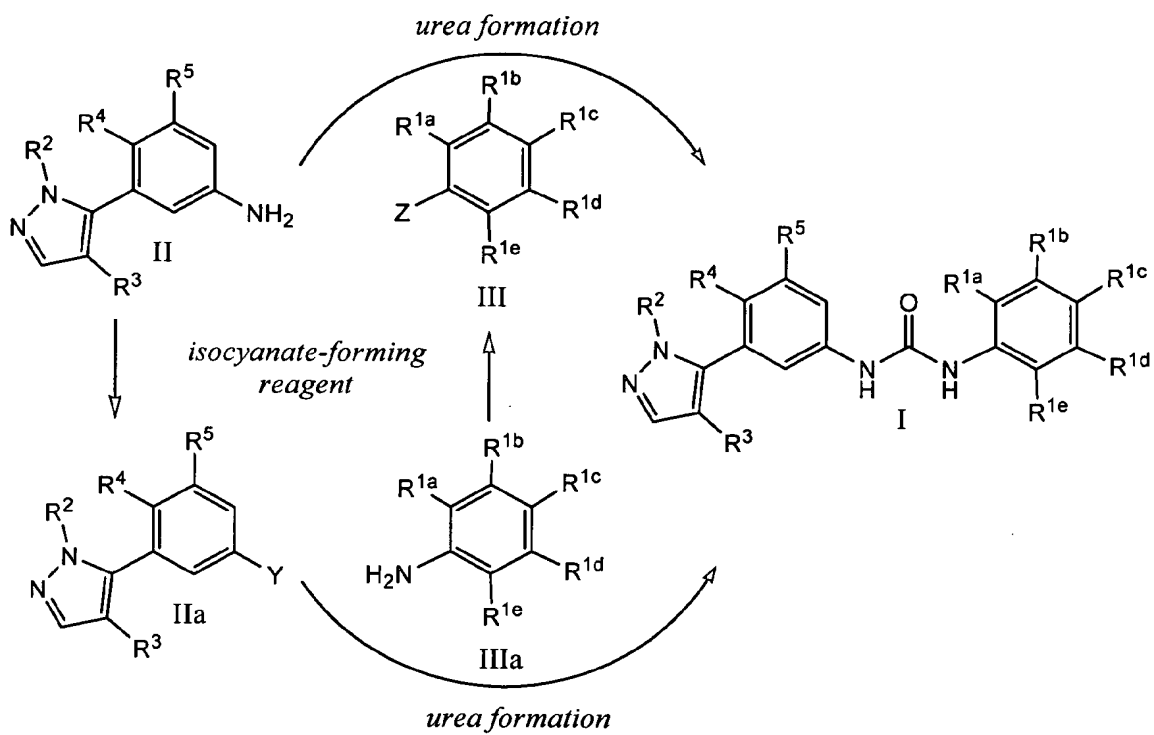
wherein constituent members are provided herein.

5 DETAILED DESCRIPTION

The present invention is directed to processes and intermediates for the preparation of substituted phenylpyrazole ureas that are useful as 5-HT_{2A} serotonin receptor modulators for the treatment of disorders mediated by 5-HT_{2A} serotonin receptor expression and/or activity such as, for example, central nervous system disorders (e.g.,
10 dementia, behavioral disorders, psychoses, Gilles de la Tourette's syndrome, manic disorder, schizophrenia, and the like), cardiovascular disorders (e.g., coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, and the like) and other disorders.

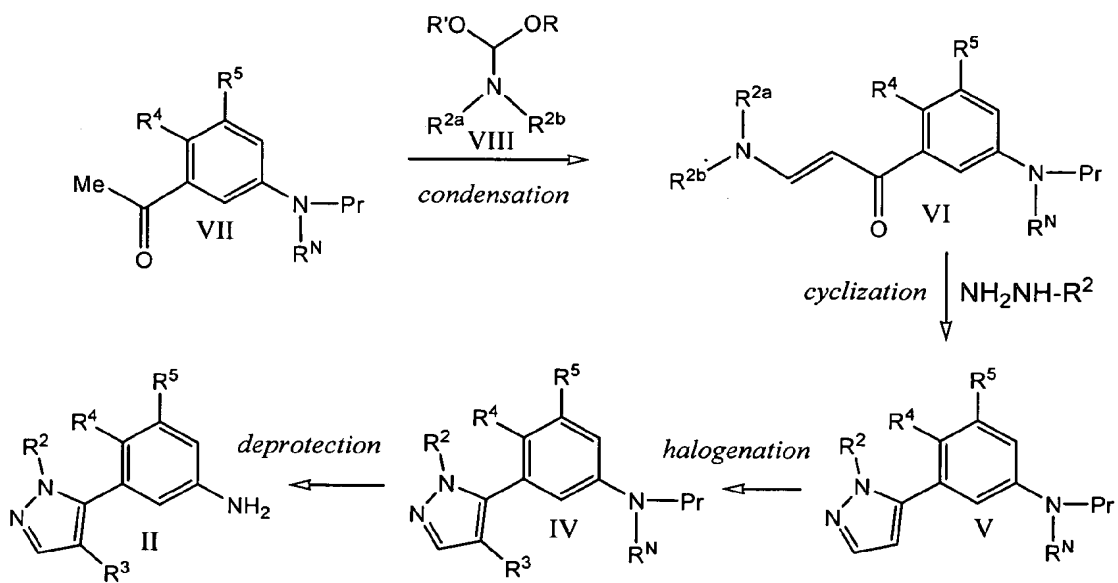
Example processes and intermediates of the present invention are provided below
15 in Schemes Ia and Ib, wherein constituent members of the compounds depicted therein are defined below.

Scheme 1a



5

Scheme Ib



In a first aspect of the invention are provided processes, such as are exemplified by Schemes Ia and Ib, that involve compounds of Formulas I, II, IIa, III, IIIa, IV, V, VI, VII and VIII, or salt forms thereof, wherein:

R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 , SR^7 , SOR^8 , SO_2R^8 , COR^8 , $COOR^7$, $OC(O)R^8$, NR^9R^{10} , carbocyclyl optionally substituted by one or more R^6 or heterocyclyl optionally substituted by one or more R^6 ; or R^{1a} and R^{1b} , R^{1b} and R^{1c} , R^{1c} and R^{1d} , or R^{1d} and R^{1e} together with the carbon atoms to which they are attached form a fused C_{5-7} cycloalkyl group or fused C_{5-7} heterocycloalkyl group; wherein each of said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, is optionally substituted with one or more C_{1-6} acyl, C_{1-6} acyloxy, C_{1-6} alkoxy, C_{1-6} thioalkoxy, carboxamide, C_{1-6} alkylcarboxamide, C_{2-8} dialkylcarboxamide, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylureido, amino, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-6} alkoxycarbonyl, carboxy, cyano, C_{3-7} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} halothioalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, mercapto or nitro;

R^2 is C_{1-4} alkyl;

R^3 is F, Cl, Br or I;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, $(C_{1-6}$ alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R^6 is halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, $(C_{1-4}$ alkyl)amino, $di(C_{1-4}$ alkyl)amino, hydroxy, carboxy, $(C_{1-4}$ alkoxy)carbonyl, C_{1-4} acyl, C_{1-4} acyloxy, aminocarbonyl, $(C_{1-4}$ alkyl)aminocarbonyl, or $di(C_{1-4}$ alkyl)aminocarbonyl;

R^7 and R^{11} are each, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, $(C_{3-7}$ cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R^8 and R^{12} are each, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino,

5 R^9 and R^{10} are each, independently, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C_{1-8} alkyl)carbonyl, (C_{1-8} haloalkyl)carbonyl, (C_{1-8} alkoxy)carbonyl, (C_{1-8} haloalkoxy)carbonyl, (C_{1-4} alkyl)sulfonyl, (C_{1-4} haloalkyl)sulfonyl or arylsulfonyl;

10 or R^9 and R^{10} , together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

R^{13} and R^{14} are each, independently, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C_{1-8} alkyl)carbonyl, (C_{1-8} haloalkyl)carbonyl, (C_{1-8} alkoxy)carbonyl, (C_{1-8} haloalkoxy)carbonyl, (C_{1-4} alkyl)sulfonyl, (C_{1-4} haloalkyl)sulfonyl or arylsulfonyl;

or R^{13} and R^{14} , together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

Pr is an amino protecting group;

20 R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;

R^{2a} and R^{2b} are each, independently, C_{1-4} alkyl;

R and R' are each, independently, C_{1-6} alkyl, arylalkyl or alkylaryl, or R and R' together with the O atoms to which they are attached and the intervening CH group form a 5- or 6-membered heterocycloalkyl group;

Y is an isocyanate group ($-NCO$) or isocyanate equivalent; and

Z is an isocyanate group ($-NCO$) or isocyanate equivalent.

30 In some embodiments, at least one of R^4 and R^5 is other than H.

In some embodiments, R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 , SR^7 , SOR^8 , SO_2R^8 , COR^8 , $COOR^7$, $OC(O)R^8$, NR^9R^{10} , carbocyclyl optionally substituted by one or more R^6 or heterocyclyl optionally substituted by one or more R^6 .

In some embodiments, R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 or carbocyclyl optionally substituted by one or more R^6 .

In some embodiments, R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo,
5 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments, R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, F, Cl, Br, or I.

In some embodiments, R^{1a} is H or halo, R^{1b} is H, R^{1c} is halo, R^{1d} is H, and R^{1e} is H.

In some embodiments, R^{1a} is halo, R^{1b} is H, R^{1c} is halo, R^{1d} is H, and R^{1e} is H.

10

In some embodiments:

R^{1a} is F, R^{1b} is H, R^{1c} is F, R^{1d} is H, and R^{1e} is H;

R^{1a} is H, R^{1b} is H, R^{1c} is Cl, R^{1d} is H, and R^{1e} is H;

R^{1a} is H, R^{1b} is H, R^{1c} is F, R^{1d} is H, and R^{1e} is H; or

15 R^{1a} is H, R^{1b} is H, R^{1c} is Cl, R^{1d} is H, and R^{1e} is H.

In some embodiments, R^2 is methyl or ethyl.

In some embodiments, R^2 is methyl.

In some embodiments, R^3 is Cl or Br.

20 In some embodiments, R^3 is Br.

In some embodiments, R^4 is other than H.

In some embodiments, R^4 is H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

30 In some embodiments, R^4 is C_{1-6} alkoxy optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide,

halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

In some embodiments, R⁴ is C₁₋₆ alkoxy.

In some embodiments, R⁴ is C₁₋₃ alkoxy.

5 In some embodiments, R⁴ is methoxy or ethoxy.

In some embodiments, R⁴ is methoxy.

In some embodiments, R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

In some embodiments, R⁵ is H.

10 In some embodiments, R and R' are both C₁₋₄ alkyl.

In some embodiments, R and R' are both methyl.

In some embodiments, R^{2a} and R^{2b} are both methyl.

In some embodiments, Pr is an acyl group.

In some embodiments, Pr is -C(O)-(C₁₋₄ alkyl).

15 In some embodiments, Pr is -C(O)Me.

In some embodiments:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each, independently, H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR⁷, SR⁷, SOR⁸, SO₂R⁸, COR⁸, COOR⁷,

20 OC(O)R⁸, NR⁹R¹⁰, carbocyclyl optionally substituted by one or more R⁶ or heterocyclyl optionally substituted by one or more R⁶;

R³ is F, Cl, Br or I;

R⁴ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅

25 acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄

alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄

haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄

30 halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

R² is methyl;
R³ is Br;
R⁴ is methoxy; and
R⁵ is H.

5

In some embodiments:

R^{1a} is H;

R^{1b} is H;

R^{1c} is Cl;

10

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Br;

R⁴ is methoxy; and

15

R⁵ is H.

In some embodiments:

R^{1a} is H;

R^{1b} is H;

20

R^{1c} is F;

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Br;

25

R⁴ is methoxy; and

R⁵ is H.

In some embodiments:

R^{1a} is H;

30

R^{1b} is H;

R^{1c} is Cl;

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Cl;

R⁴ is methoxy; and

R⁵ is H.

5 In some embodiments, Z is -NCO.

In some embodiments, Y is -NCO.

In some embodiments:

R³ is F, Cl, Br or I;

10 R⁴ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl,
 15 carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or
 20 C₁₋₆ alkoxy.

In some embodiments:

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy group optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;
 30 and

R⁵ is H.

In some embodiments:

R² is methyl or ethyl;

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy; and

R⁵ is H.

5

In some embodiments:

R² is methyl;

R³ is Cl or Br;

R⁴ is methoxy; and

10

R⁵ is H.

In some embodiments, for compounds of Formula II, R² is methyl; R³ is Cl or Br; R⁴ is methoxy; and R⁵ is H.

15 In some embodiments, for compounds of Formula IV, R² is methyl; R³ is Br; R⁴ is methoxy; R⁵ is H; and Pr is -C(O)Me.

In some embodiments, for compounds of Formula IV, R² is methyl; R³ is Cl; R⁴ is methoxy; R⁵ is H; and Pr is -C(O)Me.

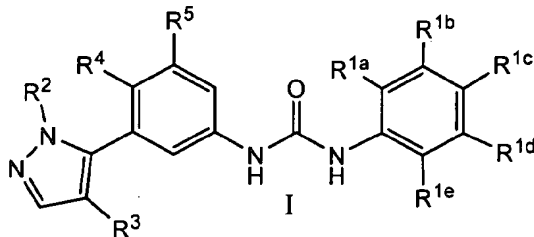
In some embodiments, for compounds of Formula V, R² is methyl; R⁴ is methoxy; R⁵ is H; and Pr is -C(O)Me.

20

In some embodiments, for compounds of Formula VI, R^{2a} is methyl; R^{2b} is methyl; R⁴ is methoxy; R⁵ is H; and Pr is -C(O)Me.

Urea Forming Step

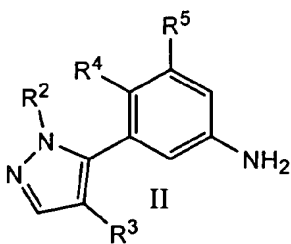
25 The chemical reactions resulting in compounds of Formula I and formation of the urea linkage can be carried out by any of numerous methods known in the art. Example urea-forming processes according to the present invention are depicted in Scheme Ia. Accordingly, the compound of Formula I:



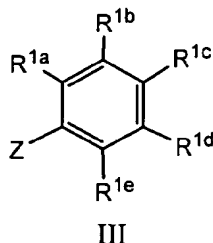
wherein constituent members are defined herein, can be prepared by:

30

reacting a compound of Formula II:

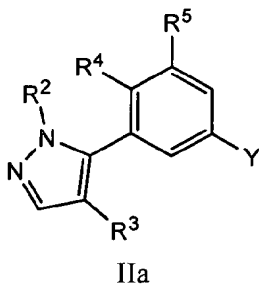


with a compound of Formula III:



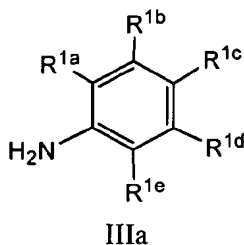
- 5 wherein Z is an isocyanate group ($-NCO$) or isocyanate equivalent, for a time and under conditions suitable for forming the compound of Formula I; or

reacting a compound of Formula II with an isocyanate-generating reagent for a time and under conditions suitable for forming a compound of Formula IIa:



10

wherein Y is an isocyanate group or isocyanate equivalent; and reacting the compound of Formula IIa with a compound of Formula IIIa:



- 15 for a time and under conditions suitable for forming the compound of Formula I.

In some embodiments, the reactants bearing the isocyanate or isocyanate equivalent groups (e.g., compounds of Formula IIa or III) are provided in excess relative to the amount of aniline (e.g., compounds of Formula II or IIIa). For example, the molar ratio of a compound of Formula II to a compound of Formula III, or the molar ratio of a

compound of Formula IIIa to a compound of Formula IIa, can be about 1:1 to about 1:1.5 or about 1:1 to about 1:1.2. In further embodiments, the compound having the isocyanate or isocyanate equivalent moieties can be added to a solution containing the aniline. The addition can be, for example, carried out in a portionwise manner.

5 The urea formation step can be optionally carried out in the presence of organic solvent such as an aromatic solvent (e.g., benzene, toluene, etc.), N,N-dimethylformamide (DMF), methylsulfoxide, acetonitrile, ethyl acetate, methylene chloride, mixtures thereof and the like. In some embodiments, the reaction solvent contains toluene.

10 The urea-forming reaction can be carried out at any temperature. For example, suitable temperatures can be from about 0 to about 60 °C or about 10 to about 45 °C. In some embodiments, the reaction is carried out at a reduced temperature such as about 10 to about 20 °C. In some embodiments, urea formation is carried out under an inert atmosphere.

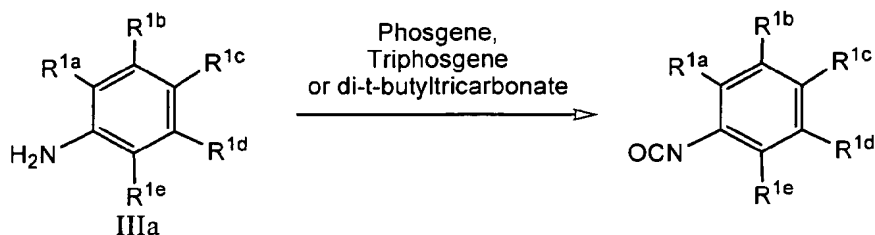
15 In some embodiments, the aniline starting material (e.g., a compound of Formula II or IIIa) can be dissolved in an aromatic solvent prior to the reacting, forming a solution. The aromatic solvent can be refluxed for a time and under conditions to at least partially remove residual water optionally present in the solution. Removal of water is believed to diminish formation of unwanted byproducts and increase yields. In some embodiments, the water present in the solution after refluxing is less than about 5, less than about 3, less than about 1, less than about 0.1, less than about 0.03 or less than about 0.01 % by volume.

20 In some embodiments, the compound of Formula I is prepared by reacting a compound of Formula II with a compound of Formula III. In alternate embodiments, the compound of Formula I is prepared by reacting a compound of Formula IIa with a compound of Formula IIIa.

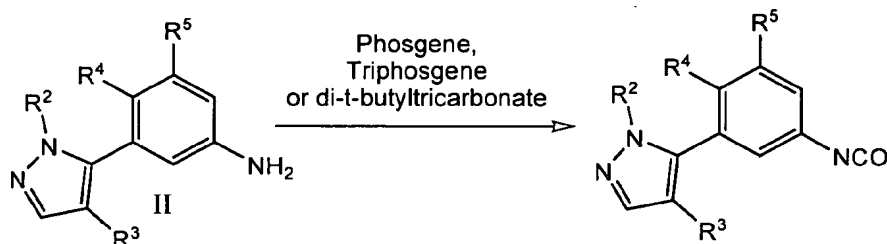
25 Starting materials bearing isocyanate and isocyanate equivalent moieties are well known in the art and commercially available. These can also be routinely prepared from corresponding anilines by reaction with an isocyanate-generating reagent, which includes materials that react with the amino group of an aniline to form an isocyanate equivalent group. For example, an isocyanate-bearing compound can be readily prepared by reacting the corresponding aniline with an isocyanate-generating reagent such as, for example, phosgene (i.e., $\text{Cl}_2\text{C}=\text{O}$) or triphosgene [i.e., bis-trichloromethyl carbonate, $\text{Cl}_3\text{COC}(\text{O})\text{OCCl}_3$] to generate the isocyanate derivative which can then be optionally isolated. Another procedure for preparing isocyanates involves using the isocyanate-

generating reagent di-*t*-butyltricarboxylate to generate isocyanates from anilines in a similar manner as described above. An example of this procedure is reported by Peerlings et al. in *Tetrahedron Lett.* **1999**, *40*, 1021-1024, the disclosure of which is incorporated herein by reference in its entirety. These procedures and others known in the art can give rise to isocyanates as illustrated in Schemes IIa and IIb below.

Scheme IIa

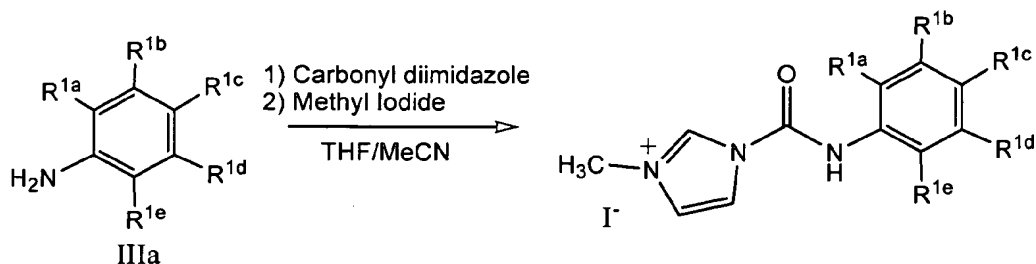


Scheme IIb

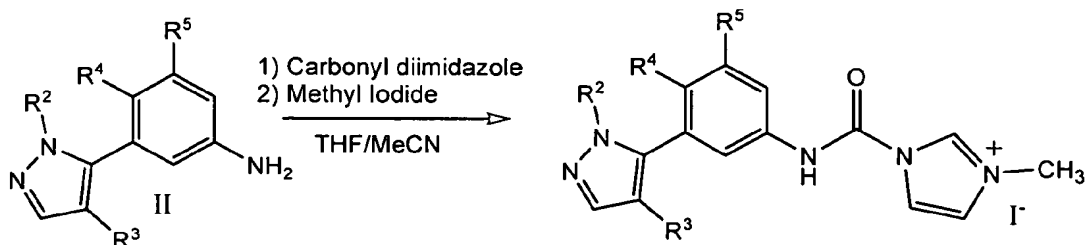


An isocyanate equivalent include a moiety other than isocyanate that is able to form a urea linkage upon reaction with an aniline (e.g., compounds of Formula II or IIIa). Isocyanate equivalents can be prepared from the corresponding anilines by the sequential action of the isocyanate-generating reagents: 1) carbonyl diimidazole and 2) methyl iodide in THF and acetonitrile, respectively, as described, for example, by Batey et al. in *Tetrahedron Lett.* **1998**, *39*, 6267-6270, the disclosure of which is incorporated herein by reference in its entirety. This procedure can give rise to isocyanate equivalents as illustrated in Schemes IIIa and IIIb below.

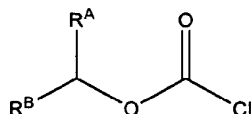
Scheme IIIa



Scheme IIIb



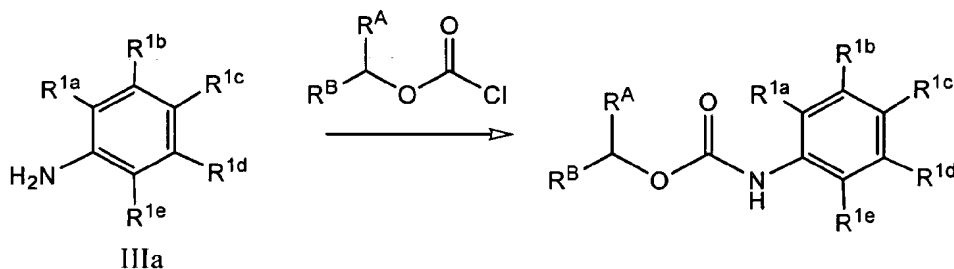
Other isocyanate equivalents can be generated by reacting the corresponding aniline with an isocyanate-generating reagent such a substituted alkyl chloroformate of Formula:



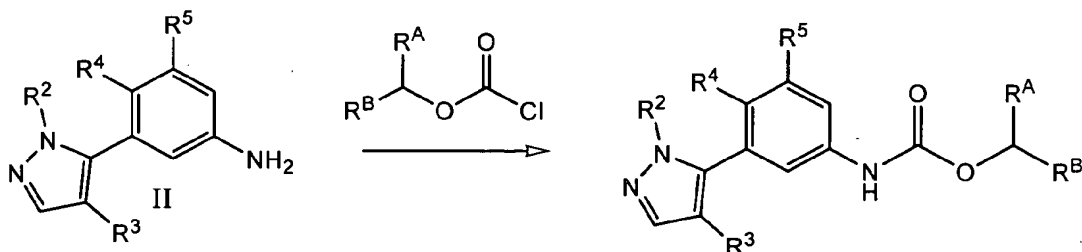
wherein R^A is C₁₋₈ alkyl and R^B is a leaving group, for a time and under conditions suitable for forming the isocyanate equivalent. In some embodiments, R^A is methyl. In further embodiments, R^B is Cl, Br, I, mesylate, tosylate or the like. In yet further embodiments, R^B is Cl, Br or I; and in yet further embodiments, R^B is Cl.

Formation of isocyanate equivalents using a substituted alkyl chloroformate is illustrated in Schemes IVa and IVb below.

Scheme IVa



Scheme IVb



Reaction of anilines (e.g., compounds of Formula II and IIIa) such as according to Schemes IVa and IVb with the isocyanate-generating reagent substituted alkylchloroformate can be optionally carried out in the presence of an organic base. Suitable organic bases include, for example, pyridine, dimethylaminopyridine, piperidine, morpholine, mixtures thereof and the like. In some embodiments, the organic base is pyridine. The organic base can, in some instances, replace the leaving group R^B to form an organic base derivative. In some embodiments, pyridine replaces the leaving group R^B to form a pyridinium derivative.

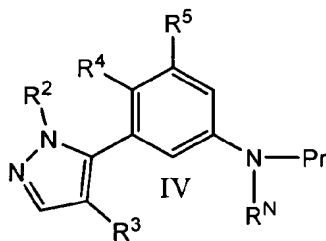
The reactions of anilines (e.g., compounds of Formula II and IIIa) with substituted alkylchloroformates can be optionally carried out in a solvent. Suitable solvents include, for example, polar solvents such as N,N-dimethylformamide (DMF), methysulfoxide, acetonitrile, ethyl acetate, tetrahydrofuran, methylene chloride and the like.

Generally, the molar ratio of an aniline such as a compound of Formula II or IIIa to a substituted alkylchloroformate can range from about 1:1 to about 1:2. In some embodiments, the ratio is about 1:1 to about 1:1.5. Such reactions can be carried out at any suitable temperature such as, for example, about 0 to about 60 °C or about 10 to about 45 °C.

It is generally understood that although the isocyanate or isocyanate equivalent can be isolated, it can also be generated *in situ* and used directly to complete the urea formation reaction. Accordingly, in some embodiments, the isocyanate or isocyanate equivalent is generated *in situ* and reacted directly with the appropriate aniline without isolation.

Deprotection

According to a further aspect of the invention, a compound of Formula II can be prepared by the process comprising reacting a compound of Formula IV:



wherein constituent members are provided herein, with a deprotecting agent for a time and under conditions suitable for forming the compound of Formula II.

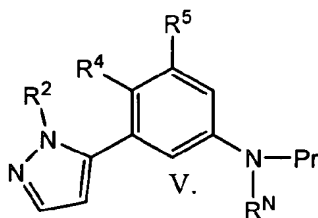
Numerous suitable deprotecting agents are known that can selectively remove an amino protecting group. The chemistry of protecting groups can be found, for example, in Green and Wuts, et al., *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, 1999, which is incorporated herein by reference in its entirety. In some embodiments, the amino protecting group (Pr) is selectively removed by hydrolysis. In further embodiments, the deprotecting agent is a base such as an inorganic base. An example deprotecting reagent is a base containing hydroxide, such as an alkali metal hydroxide including sodium hydroxide, lithium hydroxide, potassium hydroxide and the like. In some embodiments, the deprotecting agent is sodium hydroxide.

Deprotection can be optionally carried out in an organic solvent. In some embodiments, the organic solvent contain an alcohol such as methanol, ethanol, isopropanol, n-propanol, butanol, mixtures thereof or the like. In some embodiments, the organic solvent contains methanol.

Deprotection can be conducted at any suitable temperature. In some embodiments, deprotection is carried out at a temperature at or above about room temperature. In some embodiments, deprotection is carried out at about 0 to about 100, about 20 to about 100, about 30 to about 100, about 40 to about 100, about 50 to about 100 or about 70 to about 90°C. In further embodiments, deprotection is carried out at reflux temperature.

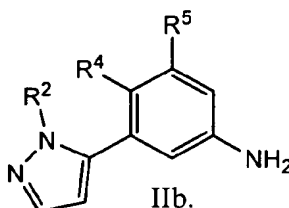
In some embodiments, the deprotecting reagent can be provided in molar excess relative to the amount of compound of Formula IV. In embodiments where the deprotecting reagent is an alkali metal hydroxide the molar ratio of alkali metal hydroxide to compound of Formula IV is about 1:1 to about 1:100, about 1:1 to about 1:10, about 1:3 to about 1:8, or about 1:4 to about 1:6.

The deprotection of compounds of Formula IV can optionally be carried out in the presence of a compound of Formula V



which can be present in batches of compound of Formula IV due to any number of reasons including, for example, incomplete halogenation of the compound of Formula V or dehalogenation of the compound of Formula IV during work up, isolation, or other

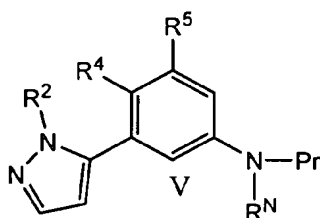
manipulations. Compositions of the starting material of Formula IV can optionally contain the compound of Formula V in any mole % such as, for example, less than about 10, less than about 8, less than about 5, less than about 4, less than about 3, less than about 2 or less than about 1 mole %. Deprotection of a compound of Formula V can result in
5 formation of the corresponding non-halogenated (i.e. lacking R³), free amine of Formula IIb:



Accordingly, the product of the deprotection reaction can contain some amount of
10 compound of Formula IIb. In some embodiments, the product of the deprotection reaction contains less than about 10, less than about 8, less than about 5, less than about 4, less than about 3, less than about 2 or less than about 1 mole % of a compound of Formula IIb.

Halogenation

15 In further aspects of the inventions, a compound of Formula IV can be prepared by the process comprising reacting a compound of Formula V:



with a halogenating reagent for a time and under conditions suitable for forming the compound of Formula IV.

20 Any of numerous halogenating reagents known in the art can be used. In some embodiments, the halogenating reagent is a brominating or chlorinating reagent. Some example brominating reagents include, for example, Br₂, N-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin, pyridinium tribromide (pyrHBr₃) and the like. An example chlorinating reagent is N-chlorosuccinimide. In some embodiments, the
25 halogenating reagent is N-bromosuccinimide.

Any suitable organic solvent can be optionally used to carry out the halogenating reaction. In some embodiments, the organic solvent contains an alcohol such as methanol,

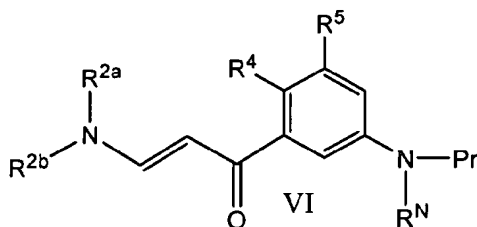
ethanol, n-propanol, isopropanol, butanol, mixtures thereof and the like. In some embodiments, the organic solvent is methanol. In further embodiments, the organic solvent includes dimethylformamide or tetrahydrofuran.

Suitable temperatures for the halogenating reaction can vary. For example, the reaction temperature can be at or below about room temperature such as, for example, from about 0 to about 25 °C.

The molar ratio of halogenating reagent to compound of Formula V can be routinely selected or optimized by the skilled artisan to minimize di-halogenated by products and maximize yield of the mono-halogenated product. In some embodiments, the molar ratio is from about 1:0.8 to about 1:1.2, from about 1:0.9 to about 1:1.1, from about 1:0.95 to about 1:1.05, or about 1:1.

Cyclization

In yet further aspects of the invention, a compound of Formula V can be prepared by the process comprising reacting a compound of Formula VI:



with an alkylhydrazine having the formula $\text{NH}_2\text{NH-R}^2$ for a time and under conditions suitable for forming the compound of Formula V. In some embodiments, the alkylhydrazine methyl hydrazine ($\text{NH}_2\text{NH-Me}$).

The cyclization reaction can be optionally carried out in the presence of an organic solvent. In some embodiments, the solvent contains an alcohol such as, for example, methanol, ethanol, isopropanol, n-propanol, butanol, mixtures thereof and the like. In some embodiments, the organic solvent contains methanol. In some embodiments, the organic solvent contains ethanol. In further embodiments, excess alkylhydrazine can serve as solvent.

The cyclization reaction can further be carried out in the presence of an acid. In some embodiments, the acid is an inorganic acid such as hydrochloric acid, hydrobromic acid; or the acid is an organic acid such as acetic acid or trifluoroacetic acid. In some embodiments, the acid is hydrochloric acid. The molar ratio of the alkylhydrazine to acid is from about 1:0.1 to about 1:100; from about 1:0.1 to about 1:20, from about 1:0.5 to

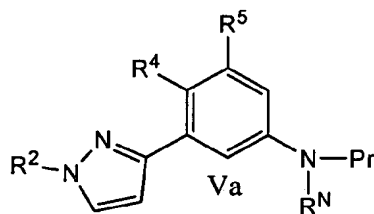
about 1:12, from about 1:1 to about 1:8, or from about 1:2 to about 1:6. In some embodiments, the molar ratio of the alkylhydrazine to acid is about 1:3. In further embodiments, the molar ratio of the alkylhydrazine to acid is above about 1:2.

The molar ratio of compound of Formula VI to alkylhydrazine can vary. In some embodiments, alkylhydrazine can be provided in molar excess. Example suitable molar ratios include about 1:1 to about 1:10, about 1:1 to about 1:5, about 1:1 to about 1:3, about 1:1 to about 1:1.5 or about 1:1 to about 1:1.2.

The cyclization reaction can be carried out at any temperature. In some embodiments, the reaction temperature is at or below room temperature. In further embodiments, the reaction temperature is from about -10 to about 30 °C. In yet further embodiments, the reaction temperature is initially held at about -10 to about 0 °C, after which the temperature is then held for a period of time at about 5 to about 15 °C, after which the temperature is then held at about 20 to about 25 °C.

In some embodiments, the cyclization reaction can be conducted such that the compound of Formula VI is added to a solution containing the alkylhydrazine and optionally an acid, such as HCl.

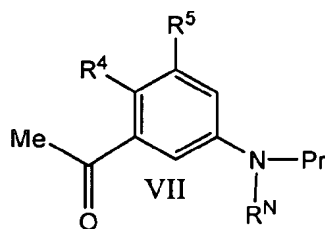
The reacting with an alkylhydrazine can optionally further produce a byproduct compound of Formula Va:



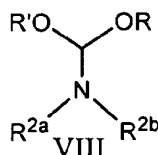
In some embodiments, the compound of Formula Va is produced in a lesser amount than the compound of Formula V. For example, the cyclization reaction can result in a product having molar ratio of compound of Formula V to compound of Formula Va that is greater than about 2, greater than about 4, or greater than about 5.

Condensation

In yet a further aspect of the present invention, a compound of Formula VI is prepared by the process comprising reacting a compound of Formula VII:



with an acetal of Formula VIII:



wherein R and R' are each, independently, C₁₋₆ alkyl, arylalkyl or alkylaryl, or R and R' together with the O atoms to which they are attached and the intervening CH group form a 5- or 6-membered heterocycloalkyl group, for a time and under conditions suitable for forming the compound of Formula VI.

The acetal of Formula VIII can be any of a variety of compounds including, for example, N,N-dimethylformamide dimethyl acetal, N,N-dimethylformamide dipropyl acetal, N,N-dimethylformamide diisopropyl acetal, N,N-dimethylformamide dibutyl acetal, N,N-dimethylformamide di-t-butyl acetal, and N,N-dimethylformamide dineopentyl acetal, N,N-dimethylformamide dicyclohexyl acetal, N,N-dimethylformamide dibenzyl acetal, N,N-dimethylformamide ethylene acetal and N,N,5,5-tetramethyl-1,3-dioxan-2-amine. In some embodiments, the acetal is N,N-dimethylformamide dimethyl acetal.

The condensation reaction can be optionally carried out in a solvent such as an organic solvent. In some embodiments, the solvent contains an alcohol such as methanol, ethanol, n-propanol, isopropanol, butanol, pentanol, mixtures thereof and the like. In some embodiments, the solvent is ethanol. In further embodiments, the solvent is methanol. In yet further embodiments, excess acetal can serve as solvent.

In some embodiments, the condensation reaction is carried out in the same solvent as the cyclization reaction. In further embodiments, the condensation reaction is carried out in the same solvent as the cyclization reaction and the product of the condensation reaction is not isolated prior to carrying out the cyclization reaction.

The condensation reaction can be carried out at any suitable temperature such as at or above room temperature. In some embodiments, the reaction temperature is from about

20 to about 95 °C, about 20 to about 85 °C, or about 20 to about 75 °C. In further embodiments, the reaction temperature is reflux temperature.

The condensation reaction can be optionally carried out such that the acetal of Formula VIII is added to a mixture of the compound of Formula VII and solvent. The mixture can be homogenous or heterogenous.

In some embodiments, the acetal is provided in molar excess relative to the amount of compound of Formula VII. Example molar ratios of said acetal to compound of Formula VII include about 1.1 to about 10, about 1.2 to about 5, or about 1.5 to about 3.

10 Definitions

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms.

As used herein, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Example alkenyl groups include ethenyl, propenyl, cyclohexenyl, and the like.

As used herein, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include ethynyl, propynyl, and the like.

As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF₃, C₂F₅, CHF₂, CCl₃, CHCl₂, C₂Cl₅, and the like. An alkyl group in which all of the hydrogen atoms are replaced with halogen atoms can be referred to as "perhaloalkyl."

As used herein, "carbocyclyl" refers to groups that are saturated (i.e., containing no double or triple bonds) or unsaturated (i.e., containing one or more double or triple bonds) cyclic hydrocarbon moieties. Carbocyclyl groups can be mono- or polycyclic. Example carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

cyclopentenyl, 1, 3-cyclopentadienyl, cyclohexenyl, norbornyl, norpinyl, norcarnyl, adamantyl, phenyl, and the like. Carbocyclyl groups can be aromatic (e.g., "aryl") or non-aromatic (e.g., "cycloalkyl"). In some embodiments, carbocyclyl groups can have from 3 to about 20, 3 to about 10, or 3 to about 7 carbon atoms.

5 As used herein, "aryl" refers to monocyclic or polycyclic aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

10 As used herein, "cycloalkyl" refers to non-aromatic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono-, bi- or poly-cyclic ring systems as well as double and triple bonds. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of pentane, hexane, and the like.

15 As used herein, "heterocyclyl" refers to a group that can be a saturated or unsaturated carbocyclyl group wherein one or more of the ring-forming carbon atoms of the carbocyclyl group is replaced by a heteroatom such as O, S, or N. Heterocyclyl groups can be aromatic (e.g., "heteroaryl") or non-aromatic (e.g., "heterocycloalkyl").

20 Heterocyclyl groups can correspond to hydrogenated and partially hydrogenated heteroaryl groups. Heterocarbocyclyl groups can contain, in addition to at least one heteroatom, from about 1 to about 20, about 2 to about 10, or about 2 to about 7 carbon atoms and can be attached through a carbon atom or heteroatom. In some embodiments, heterocyclyl groups can have from 3 to 20, 3 to 10, 3 to 7, or 5 to 7 ring-forming atoms.

25 Further, heterocyclyl groups can be substituted or unsubstituted. Examples of heterocyclyl groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like as well as any of the groups listed for heteroaryl

30 and heterocycloalkyl.

As used herein, "heteroaryl" groups are monocyclic and polycyclic aromatic hydrocarbons that have at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl,

pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-S-oxide, 2,3-dihydrobenzothienyl-S-dioxide, benzoxazolin-2-on-yl, indoliny, benzodioxolanyl, benzodioxane, and the like. In some embodiments, heteroaryl groups can have from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, heteroaryl groups have 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to a cycloalkyl group wherein one or more of the ring-forming carbon atoms is replaced by a heteroatom such as an O, S, N, or P atom. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl pyromellitic diimidyl, phthalanyl, and benzo derivatives of saturated heterocycles such as indolene and isoindolene groups.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "alkoxy" refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, "haloalkoxy" refers to alkoxy substituted by at least one halo.

As used herein, "thioalkoxy" refers to an alkoxy group in which the O atom is replaced by an S atom.

As used herein, "halothioalkoxy" refers to thioalkoxy substituted by at least one halo.

As used herein, "acyl" refers to a carbonyl group substituted by H, alkyl, alkenyl, alkynyl or carbocyclyl. Example acyl groups include formyl or acetyl.

As used herein, "acyloxy" refers to -O-acyl.

As used herein, "carboxamide" or "aminocarbonyl" refers to -C(O)NH₂.

As used herein, "alkylcarboxamide" or "alkylaminocarbonyl" refers to -C(O)NH(alkyl).

As used herein, "dialkylcarboxamide" or "dialkylaminocarbonyl" refers to -C(O)N(alkyl)₂.

As used herein, "sulfonamide" refers to -S(O)NH₂.

As used herein, "alkylsulfonamide" refers to -S(O)NH(alkyl).

As used herein, "dialkylsulfonamide" refers to $-S(O)N(alkyl)_2$.

As used herein, "sulfonyl" refers to SO_2 .

As used herein, "sulfinyl" refers to SO .

As used herein, "alkylsulfinyl" refers to sulfinyl substituted by alkyl.

5 As used herein, "haloalkylsulfinyl" refers to sulfinyl substituted by haloalkyl.

As used herein, "arylsulfinyl" refers to sulfinyl substituted by aryl.

As used herein, "alkylsulfonyl" refers to sulfonyl substituted by alkyl.

As used herein, "haloalkylsulfonyl" refers to sulfonyl substituted by haloalkyl.

As used herein, "arylsulfonyl" refers to sulfonyl substituted by aryl.

10 As used herein, "uerido" refers to $-NHC(O)NH_2$.

As used herein, "alkyluserido" refers to ureido substituted by an alkyl group.

As used herein, "amino" refers to NH_2 .

As used herein, "alkylamino" refers to amino substituted by alkyl.

As used herein, "dialkylamino" refers to amino substituted by two alkyl groups.

15 As used herein, "alkoxycarbonyl" refers to $-CO-(alkoxy)$.

As used herein, "haloalkoxycarbonyl" refers to $-CO-(haloalkoxy)$.

As used herein, "carbocyclalkyl" refers to alkyl substituted by carbocycl.

As used herein, "arylalkyl" refers to an alkyl moiety substituted by an aryl group.

Example aralkyl groups include benzyl, phenethyl, and naphthylmethyl groups. In some

20 embodiments, arylalkyl groups have from 7 to 20 or 7 to 11 carbon atoms.

As used herein, "heterocyclalkyl" refers to alkyl substituted by heterocycl.

As used herein, "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, the term "reacting" is used as known in the art and generally refers
25 to the bringing together of chemical reagents in such a manner so as to allow their interaction at the molecular level to achieve a chemical or physical transformation of at least one chemical reagent.

As used herein, the term "substituted" refers to the replacement of a hydrogen moiety with a non-hydrogen moiety in a molecule or group.

30 As used herein, the term "leaving group" refers to a moiety that can be displaced by another moiety, such as by nucleophilic attack, during a chemical reaction. Leaving groups are well known in the art and include, for example, halogen, hydroxy, alkoxy, $-O(CO)R^a$, $-OSO_2-R^b$, and $-Si(R^c)_3$ wherein R^a can be C_1-C_8 alkyl, C_3-C_7 cycloalkyl, aryl, heteroaryl, or heterocycloalkyl, wherein R^b can be C_1-C_8 alkyl, aryl (optionally substituted

by one or more halo, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy), or heteroaryl (optionally substituted by one or more halo, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy), and wherein R^c can be C₁-C₈ alkyl. Example leaving groups include chloro, bromo, iodo, mesylate, tosylate, trimethylsilyl, and the like.

As used herein, the term "amino protecting group" refers to a non-hydrogen amino substituent that reversibly preserves a reactively susceptible amino functionality while reacting other functional groups on the compound. A "cyclic amino protecting group" refers to an amino protecting group that includes the protected amino moiety in a ring, such as a phthalimido group or the like. Examples of amino-protecting groups include formyl, acetyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, t-butoxycarbonyl, 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-tolyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-tolylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl (Fmoc), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule. In some embodiments, the amino-protecting groups are t-butoxycarbonyl (t-Boc), allyloxycarbonyl and benzyloxycarbonyl (CbZ). In further embodiment, the amino protecting group is an acyl group such as formyl or acetyl. Further examples of

amino protecting groups are found in E. Haslam, *Protecting Groups in Organic Chemistry*, (J. G. W. McOmie, ed., 1973), at Chapter 2; and T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, (1991), at Chapter 7.

As used herein, the phrase "substantially undetectable amount" refers to an amount of compound that is either absent from a composition or present in the composition in an amount that is either not detectable by routine analytical means or is detected in an amount less than about 0.5 mole % compared with the major component of the composition.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

In some embodiments, preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, et al., *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, 1999, which is incorporated herein by reference in its entirety.

The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected. In some embodiments, reactions can be carried out in the absence of solvent, such as when at least one of the reagents is a liquid or gas.

Suitable solvents can include halogenated solvents such as carbon tetrachloride, bromodichloromethane, dibromochloromethane, bromoform, chloroform, bromochloromethane, dibromomethane, butyl chloride, dichloromethane, tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1-dichloroethane, 2-chloropropane, hexafluorobenzene, 1,2,4-trichlorobenzene, o-dichlorobenzene, chlorobenzene, fluorobenzene, fluorotrichloromethane,

chlorotrifluoromethane, bromotrifluoromethane, carbon tetrafluoride, dichlorofluoromethane, chlorodifluoromethane, trifluoromethane, 1,2-dichlorotetrafluoroethane and hexafluoroethane.

5 Suitable ether solvents include: dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, or t-butyl methyl ether.

10 Suitable protic solvents can include, by way of example and without limitation, water, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3- pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol.

15 Suitable aprotic solvents can include, by way of example and without limitation, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide, acetonitrile, dimethyl sulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl ketone, ethyl acetate, sulfolane, N,N-
20 dimethylpropionamide, tetramethylurea, nitromethane, nitrobenzene, or hexamethylphosphoramide.

Suitable hydrocarbon solvents include benzene, cyclohexane, pentane, hexane, toluene, cycloheptane, methylcyclohexane, heptane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene.

25 Supercritical carbon dioxide can also be used as a solvent.

The reactions of the processes described herein can be carried out at appropriate temperatures which can be readily determined by the skilled artisan. Reaction temperatures will depend on, for example, the melting and boiling points of the reagents and solvent, if present; the thermodynamics of the reaction (e.g., vigorously exothermic
30 reactions may need to be carried out at reduced temperatures); and the kinetics of the reaction (e.g., a high activation energy barrier may need elevated temperatures). "Elevated temperature" refers to temperatures above room temperature (about 25 °C) and "reduced temperature" refers to temperatures below room temperature.

The reactions of the processes described herein can be carried out in air or under an inert atmosphere. Typically, reactions containing reagents or products that are substantially reactive with air can be carried out using air-sensitive synthetic techniques that are well known to the skilled artisan.

5 In some embodiments, preparation of compounds can involve the addition of acids or bases to effect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

Example acids can be inorganic or organic acids. Inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and nitric acid.
10 Organic acids include formic acid, acetic acid, propionic acid, butanoic acid, methanesulfonic acid, p-toluene sulfonic acid, benzenesulfonic acid, trifluoroacetic acid, propiolic acid, butyric acid, 2-butyric acid, vinyl acetic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid and decanoic acid.

Example bases include lithium hydroxide, sodium hydroxide, potassium
15 hydroxide, lithium carbonate, sodium carbonate, and potassium carbonate. Some example strong bases include, but are not limited to, hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines, wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride,
20 potassium hydride and lithium hydride; and metal dialkylamides include sodium and potassium salts of methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, trimethylsilyl and cyclohexyl substituted amides.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended
25 unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis.

30 The processes described herein can be stereoselective such that any given reaction starting with one or more chiral reagents enriched in one stereoisomer forms a product that is also enriched in one stereoisomer. The reaction can be conducted such that the product of the reaction substantially retains one or more chiral centers present in the starting materials. The reaction can also be conducted such that the product of the reaction

contains a chiral center that is substantially inverted relative to a corresponding chiral center present in the starting materials.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

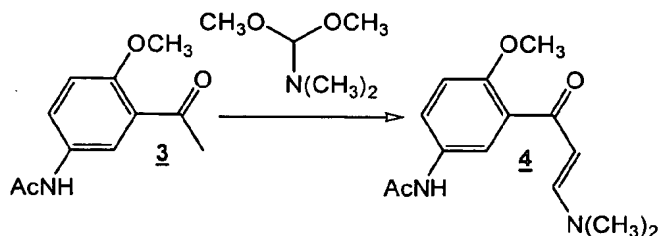
The present invention also includes salt forms of the compounds described herein. Examples of salts (or salt forms) include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. Generally, the salt forms can be prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference in its entirety.

Upon carrying out preparation of compounds according to the processes described herein, the usual isolation and purification operations such as concentration, filtration, extraction, solid-phase extraction, recrystallization, chromatography, and the like may be used, to isolate the desired products.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

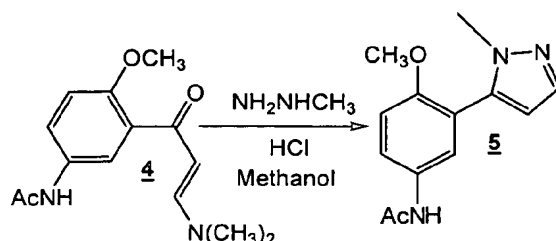
Example 1



Preparation of 3-dimethylamino-1-(2'-methoxy-5'-acetamidophenyl)prop-2-en-1-one (**4**).

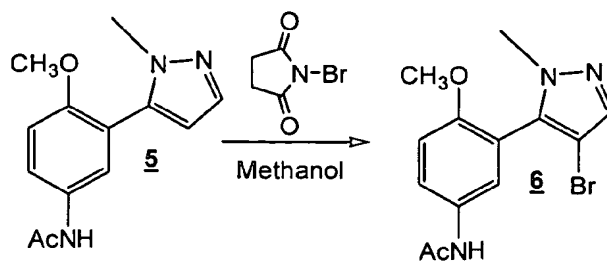
Dimethylformamide dimethyl acetal (693.3 g) was added to a suspension of 2'-methoxy-5'-acetamidoacetophenone (**3**, 1215.1 g) in ethanol (12.15 L) stirred under nitrogen at 22° C. After the resulting suspension had been stirred and refluxed under nitrogen for 18 hours, all solids had dissolved, and additional dimethylformamide dimethyl acetal (346.2 g) was added to homogeneous reaction mixture. Stirring and refluxing under nitrogen were continued for an additional 30 hours, after which additional dimethylformamide dimethyl acetal (346.2 g) was added. The reaction mixture was then stirred and refluxed under nitrogen for a final 17.5 hours, after which the reaction mixture was rotary evaporated at <45° C and <50 mm HgA to a solid residue that was dried further overnight at <45° C and <1 mm HgA to provide brown solid **4** (1547.9 g, 100.6% yield). LC/MS analyses revealed 98.3% and 100% conversion of **3** to **4** before and after evaporation of solvent, respectively.

Example 2

Preparation of 5-(2'-methoxy-5'-acetamidophenyl)-1-methyl-1H-pyrazole (**5**).

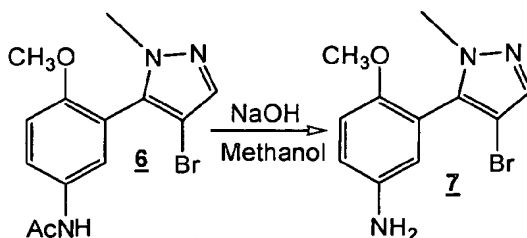
Methylhydrazine (319.3 g) was added to methanol (13.931 L) stirred and chilled to
 5 -15° C under nitrogen. Aqueous HCl (37 wt %, 1859.6 g) was then added at a rate
 sufficiently slow to enable the stirred solution to be maintained at -12 to -7° C with reactor
 jacket cooling. As stirring under nitrogen was continued at -10° C, 3-dimethylamino-1-
 (2'-methoxy-5'-acetamidophenyl)prop-2-en-1-one (**4**, 1546.9 g) was added as a solid over
 ten minutes. The resulting homogenous dark brown solution was stirred under nitrogen
 10 first at 0° C for 3 hours and then at 10° C for 5.5 hours before 33% aqueous ammonia
 (1090 mL) was added at a rate sufficiently slow (25 minutes) to enable the stirred solution
 to be maintained at 8.6-15.2° C with reactor jacket cooling. LC/MS analyses of the
 reaction mixture before aqueous ammonia treatment revealed 97.3% conversion of **4** to **5**
 and its other N-methylpyrazole isomer (in 83.3:13.2 ratio) and, after aqueous ammonia
 15 treatment, 100% conversion of **4** to **5** and its other N-methylpyrazole isomer (in 87.8:12.2
 ratio). The aqueous ammonia addition raised the reaction mixture pH to 8. Methanol (ca.
 12 L) was then distilled off the stirred reaction mixture at atmospheric pressure and
 internal temperatures rising to 74.4° C. Product crystallization, which started at the end of
 the distillation, was completed by cooling the reaction mixture to -2° C and holding that
 20 temperature with stirring for 44 hours. LC/MS analysis of the crystallization mixture's
 liquid phase revealed **5** and its other N-methylpyrazole isomer in about 1:3 ratio. (Higher
 ratios of **5** : other isomer in the liquid phase jeopardize product yield, and lower ratios
 jeopardize product purity. In either case, the crystallization can be repeated by heating the
 stirred mixture back to reflux at atmospheric pressure and, prior to recrystallization, either
 25 distilling off more methanol (if the ratio is high) or adding additional methanol (if the ratio
 is low).) The reaction mixture was filtered by suction, and the filtered solids were washed
 with 0° C water (3 L, then 2 x 500 mL) and dried at 40° C, <1 mm HgA to provide **5**
 (1157.7 g, 80.0% yield).

Example 3

**Preparation of 5-(2'-Methoxy-5'-acetamidophenyl)-4-bromo-1-methyl-1H-pyrazole (6).**

To a solution of 5-(2'-methoxy-5'-acetamidophenyl)-1-methyl-1H-pyrazole (**5**, 1141.8 g) in methanol (13.75 L) stirred under nitrogen was added solid N-bromosuccinimide (911.5 g) portionwise at a rate sufficiently slow to enable the reaction mixture to be maintained at 13.5-22.5° C with reactor jacket cooling. Bromopyrazole **6** started to precipitate about three-quarters the way through the addition, which took about 20 minutes to complete. After 30 minutes of continued stirring at 22° C, LC/MS analysis of the reaction slurry revealed complete conversion of **5** to **6**; there was no detectable starting material **5**. The stirred reaction mixture was then distilled to substantial dryness at 10 mm HgA and internal temperatures up to 30° C. The resulting solid residue was broken up, slurried in a solution of sodium hydroxide (482.25 g) in water (11.538 L) at 25° C for one hour to remove succinimide byproduct, filtered by suction, washed with water (2 x 1000 mL), and dried at 22° C and ca. 10 mm HgA to provide **6** (1385.7 g, 91.8% crude yield) containing ca. 3.2 mole % **5** as the only significant impurity.

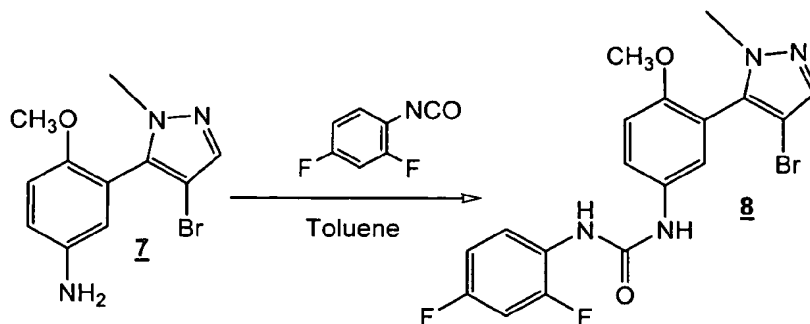
Example 4

**Preparation of 5-(2'-methoxy-5'-aminophenyl)-4-bromo-1-methyl-1H-pyrazole (7).**

The 5-(2'-methoxy-5'-acetamidophenyl)-4-bromo-1-methyl-1H-pyrazole (**6**, 1385.7 g) from the previous example, which was contaminated with ca. 3.2 mole % **5**, was slurried in methanol (13.3 L) at 22° C under nitrogen. To the resulting suspension stirred at 22° C under nitrogen was added solid N-bromosuccinimide (136.7 g total) in three

portions. The first portion of N-bromosuccinimide (68.3 g) left ca. 2.8 mole % unreacted 5 after 80 minutes. Then the second portion of N-bromosuccinimide (34.2 g) left ca. 1.8 mole % unreacted 5 after an additional 60 minutes. Then, after the third portion of N-bromosuccinimide (34.2 g) was added, conversion of 5 to 6 was complete within 15 minutes. There was no detectable starting material 5. Aqueous sodium hydroxide (50 wt %; 2606.8 g) was then added to the stirred suspension of 6 over 35 minutes at a rate sufficiently slow to enable the reaction mixture to be maintained at 10.4-24° C with reactor jacket cooling. After the addition of aqueous sodium hydroxide, a reaction mixture sample was found to contain debrominated 5 in about 2.5 mole % of the amount of 6. Methanol (about 12 L) was then distilled off the stirred reaction mixture over eight hours at 10 mm HgA and internal temperatures rising to 84° C. LC/MS analysis of the reaction mixture, now about 5.5 L of a thick but stirrable suspension, showed complete hydrolysis of 6 to 7 plus about 2 mole % of the desbromo analog of 7. Removal of substantially all remaining methanol (about 1.6 L) by continued distillation over four hours at 10 mm HgA and internal temperatures rising to 55° C left an unstirrable residue. Upon addition of diisopropyl ether (12 L) and water (1000 mL) and heating to 65° C, the mixture became stirrable, and the solids dissolved completely to provide two liquid phases. The lower (aqueous) phase was drained from the upper (organic) phase, which was then extracted with additional water (1000 mL). The aqueous phases were combined and extracted with more diisopropyl ether (4 L). After extraction with water (1000 mL), the second upper (organic) phase was combined with the first, and the resulting mixture was reheated to 50° C to completely dissolve all solids. The resulting diisopropyl ether solution was then cooled to -5° C with stirring over seven hours, during which time 7 crystallized. After being stirred at -5° C for five more hours, the resulting suspension was filtered by suction. The filtered solid was washed with 0° C diisopropyl ether (1.0 L) and dried at 40° C and <1 mm HgA to provide 7 (979.6 g, 81.2 % yield) of 99.2 % purity by HPLC with ca. 0.3 wt % desbromo 7 as the largest impurity. The crystallization and wash liquors were combined and evaporated first at 69° C and atmospheric pressure to 1 L volume and then at <40° C and 10 mm HgA on a rotary evaporator to provide a residue of pale yellow solid 7 (151.49 g, 12.6 % yield) of 94.3 % purity by HPLC with ca. 3.5 wt % desbromo 7 as the largest impurity.

Example 5



N-(2,4-Difluorophenyl)-N'-(4-methoxy-3-(4'-bromo-1'-methyl-1H-pyrazol-5'-yl)phenyl)urea (8).

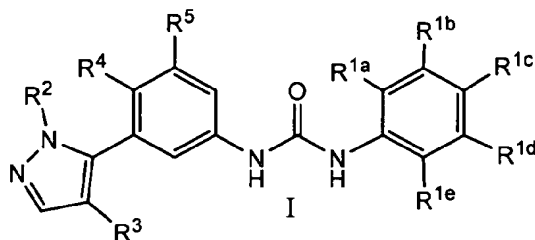
Both portions of 5-(2'-methoxy-5'-aminophenyl)-4-bromo-1-methyl-1H-pyrazole (7) from the previous example were combined by dissolution in toluene (15 L) at 27.6° C, suction filtration of the resulting solution, and rotary evaporation of the filtrate at <50° C and 10 mm HgA to a constant weight of 1127.0 g. A solution of 7 (1102.0 g of the 1127.0 g evaporation residue) in toluene (11.02 L) was stirred and refluxed at atmospheric pressure through a Dean-Stark trap under nitrogen to remove 0.8 mL of water. After the condensate had become completely clear with no further accumulation of water in the Dean-Stark trap, the toluene solution was cooled under nitrogen to 12.9° C. To the resulting solution stirred under nitrogen was added 2,4-difluorophenyl isocyanate (617.9 g) by addition funnel over 40 minutes at a rate sufficiently slow to enable the reaction mixture to be maintained at 12.9-19° C with reactor jacket cooling. Solid started to precipitate in the reaction mixture about half way through the addition. After the addition had been completed, the reaction slurry continued to be stirred at 16° C under nitrogen. Conversion of 7 to 8 was 90%, 91.2%, and 92.6% five, 60, and 120 minutes, respectively, after the addition had been completed. Three hours after the addition had been completed, a second portion of 2,4-difluorophenyl isocyanate (24.4 g) was added, and, after continued stirring of the reaction mixture at 16° C under nitrogen for an additional 30 minutes, conversion of 7 to 8 was 94%. One hour after the second addition, a third portion of 2,4-difluorophenyl isocyanate (9.7 g) was added, and, after continued stirring of the reaction mixture at 16° C under nitrogen for an additional 15 minutes, conversion of 7 to 8 was 95%. The reaction mixture was then stirred at 20° C under nitrogen for an additional 14.75 hours, after which conversion of 7 to 8 was 100%. The reaction mixture was suction filtered, and the filtered solid was washed with 2.6° C toluene (2 x 1100 mL) and dried at

100° C and pressures falling to 1 mm HgA to provide 8 (1654.9 g, 96.9 % yield) of 98.2 % purity by HPLC with ca. 0.9 mole % desbromo 8 as the largest impurity.

5 Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A process for preparing a compound of Formula I:



wherein:

R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 , SR^7 , SOR^8 , SO_2R^8 , COR^8 , $COOR^7$, $OC(O)R^8$, NR^9R^{10} , carbocyclyl optionally substituted by one or more R^6 or heterocyclyl optionally substituted by one or more R^6 ; or R^{1a} and R^{1b} , R^{1b} and R^{1c} , R^{1c} and R^{1d} , or R^{1d} and R^{1e} together with the carbon atoms to which they are attached form a fused C_{5-7} cycloalkyl group or fused C_{5-7} heterocycloalkyl group; wherein each of said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, is optionally substituted with one or more C_{1-6} acyl, C_{1-6} acyloxy, C_{1-6} alkoxy, C_{1-6} thioalkoxy, carboxamide, C_{1-6} alkylcarboxamide, C_{2-8} dialkylcarboxamide, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylureido, amino, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-6} alkoxycarbonyl, carboxy, cyano, C_{3-7} cycloalkyl, halogen, C_{1-6} haloalkoxy, C_{1-6} halothioalkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkylsulfinyl, C_{1-6} haloalkylsulfonyl, hydroxyl, mercapto or nitro;

R^2 is C_{1-4} alkyl;

R^3 is F, Cl, Br or I;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R^6 is halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, (C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino, hydroxy, carboxy, (C_{1-4} alkoxy)carbonyl,

C₁₋₄ acyl, C₁₋₄ acyloxy, aminocarbonyl, (C₁₋₄ alkyl)aminocarbonyl, or di(C₁₋₄ alkyl)aminocarbonyl;

R⁷ and R¹¹ are each, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R⁸ and R¹² are each, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino,

R⁹ and R¹⁰ are each, independently, H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C₁₋₈ alkyl)carbonyl, (C₁₋₈ haloalkyl)carbonyl, (C₁₋₈ alkoxy)carbonyl, (C₁₋₈ haloalkoxy)carbonyl, (C₁₋₄ alkyl)sulfonyl, (C₁₋₄ haloalkyl)sulfonyl or arylsulfonyl;

or R⁹ and R¹⁰, together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

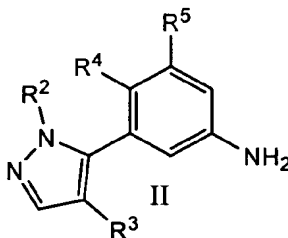
R¹³ and R¹⁴ are each, independently, H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C₁₋₈ alkyl)carbonyl, (C₁₋₈ haloalkyl)carbonyl, (C₁₋₈ alkoxy)carbonyl, (C₁₋₈ haloalkoxy)carbonyl, (C₁₋₄ alkyl)sulfonyl, (C₁₋₄ haloalkyl)sulfonyl or arylsulfonyl;

or R¹³ and R¹⁴, together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group; and

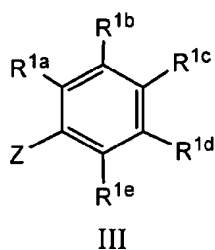
wherein at least one of R⁴ and R⁵ is other than H;

the process comprising:

a) reacting a compound of Formula II:

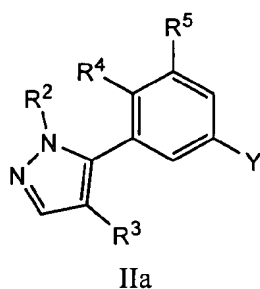


with a compound of Formula III:

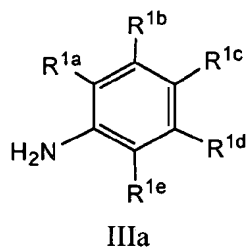


wherein Z is an isocyanate group ($-NCO$) or isocyanate equivalent, for a time and under conditions suitable for forming said compound of Formula I; or

b) reacting a compound of Formula II with an isocyanate-generating reagent for a time and under conditions suitable for forming a compound of Formula IIa:



wherein Y is an isocyanate group or isocyanate equivalent; and reacting said compound of Formula IIa with a compound of Formula IIIa:



for a time and under conditions suitable for forming said compound of Formula I.

2. The process of claim 1 wherein R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 , SR^7 , SOR^8 , SO_2R^8 , COR^8 , $COOR^7$, $OC(O)R^8$, NR^9R^{10} , carbocyclyl optionally substituted by one or more R^6 or heterocyclyl optionally substituted by one or more R^6 .

3. The process of claim 1 wherein R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^7 or carbocyclyl optionally substituted by one or more R^6 .

4. The process of claim 1 wherein R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl, or C_{1-6} haloalkyl.
5. The process of claim 1 wherein R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each, independently, H, F, Cl, Br, or I.
6. The process of claim 1 wherein R^{1a} is H or halo, R^{1b} is H, R^{1c} is halo, R^{1d} is H, and R^{1e} is H.
7. The process of claim 1 wherein R^{1a} is halo, R^{1b} is H, R^{1c} is halo, R^{1d} is H, and R^{1e} is H.
8. The process of claim 1 wherein:
 R^{1a} is F, R^{1b} is H, R^{1c} is F, R^{1d} is H, and R^{1e} is H;
 R^{1a} is H, R^{1b} is H, R^{1c} is Cl, R^{1d} is H, and R^{1e} is H;
 R^{1a} is H, R^{1b} is H, R^{1c} is F, R^{1d} is H, and R^{1e} is H; or
 R^{1a} is H, R^{1b} is H, R^{1c} is Cl, R^{1d} is H, and R^{1e} is H.
9. The process of claim 1 wherein R^2 is methyl or ethyl.
10. The process of claim 1 wherein R^2 is methyl.
11. The process of claim 1 wherein R^3 is Cl or Br.
12. The process of claim 1 wherein R^3 is Br.
13. The process of claim 1 wherein R^4 is other than H.
14. The process of claim 1 wherein R^4 is H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6}

dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

15. The process of claim 1 wherein R⁴ is C₁₋₆ alkoxy optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

16. The process of claim 1 wherein R⁴ is C₁₋₆ alkoxy.

17. The process of claim 1 wherein R⁴ is C₁₋₃ alkoxy.

18. The process of claim 1 wherein R⁴ is methoxy or ethoxy.

19. The process of claim 1 wherein R⁴ is methoxy.

20. The process of claim 1 wherein R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

21. The process of claim 1 wherein R⁵ is H.

22. The process of claim 1 wherein:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each, independently, H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, OR⁷, SR⁷, SOR⁸, SO₂R⁸, COR⁸, COOR⁷, OC(O)R⁸, NR⁹R¹⁰, carbocyclyl optionally substituted by one or more R⁶ or heterocyclyl optionally substituted by one or more R⁶;

R³ is F, Cl, Br or I;

R⁴ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino,

C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

23. The process of claim 1 wherein:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each, independently, H, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy group optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H.

24. The process of claim 1 wherein:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each, independently, H, F, Cl, Br or I;

R² is methyl or ethyl;

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy; and

R⁵ is H.

25. The process of claim 1 wherein:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each, independently, H, F, or Cl;

R² is methyl;

R³ is Cl or Br;

R⁴ is methoxy; and

R⁵ is H.

26. The process of claim 1 wherein:

R^{1a} is F;

R^{1b} is H;

R^{1c} is F;

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Br;

R⁴ is methoxy; and

R⁵ is H.

27. The process of claim 1 wherein:

R^{1a} is H;

R^{1b} is H;

R^{1c} is Cl;

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Br;

R⁴ is methoxy; and

R⁵ is H.

28. The process of claim 1 wherein:

R^{1a} is H;

R^{1b} is H;

R^{1c} is F;

R^{1d} is H;

R^{1e} is H;

R² is methyl;

R³ is Br;

R⁴ is methoxy; and

R^5 is H.

29. The process of claim 1 wherein:

R^{1a} is H;

R^{1b} is H;

R^{1c} is Cl;

R^{1d} is H;

R^{1e} is H;

R^2 is methyl;

R^3 is Cl;

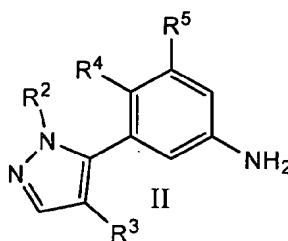
R^4 is methoxy; and

R^5 is H.

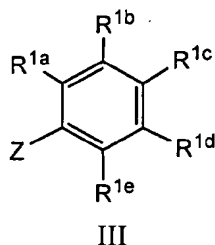
30. The process of claim 1 wherein Z is $-NCO$.

31. The process of claim 1 wherein Y is $-NCO$.

32. The process of claim 1 wherein the process comprises reacting a compound of Formula II:



with a compound of Formula III:

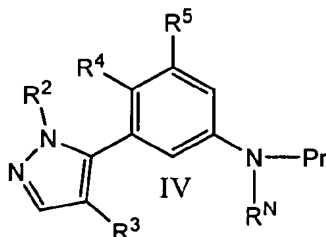


wherein Z is an isocyanate group, for a time and under conditions suitable for forming said compound of Formula I.

33. The process of claim 32 wherein said reacting is carried out in an organic solvent.
34. The process of claim 33 wherein said organic solvent comprises an aromatic solvent.
35. The process of claim 33 wherein said organic solvent comprises toluene.
36. The process of claim 33 wherein, prior to said reacting, said compound of Formula II is dissolved in said organic solvent forming a solution, wherein said organic solvent comprises toluene, and said solution is refluxed for a time and under conditions to at least partially remove residual water optionally present in said solution.
37. The process of claim 36 wherein the amount of water present in the solution after said refluxing is less than about 0.01 % by volume.
38. The process of claim 36 wherein the amount of water present in the solution after said refluxing is less than about 0.005 % by volume.
39. The process of claim 36 wherein the amount of water present in the solution after said refluxing is less than about 0.001 % by volume.
40. The process of claim 33 wherein said reacting is carried out at a reduced temperature.
41. The process of claim 40 wherein said reduced temperature is about 10 to about 20 °C.
42. The process of claim 33 wherein said reacting is carried out under an inert atmosphere.
43. The process of claim 33 wherein said compound of Formula III is added to a solution containing said compound of Formula II.
44. The process of claim 43 wherein said addition is carried out portionwise.

45. The process of claim 33 wherein said compound of Formula III is added in molar excess relative to the amount of Formula II.

46. The process of claim 1 wherein said compound of Formula II is prepared by the process comprising reacting a compound of Formula IV:



wherein:

Pr is an amino protecting group; and

R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;
with a deprotecting agent for a time and under conditions suitable for forming said compound of Formula II.

47. The process of claim 46 wherein Pr is an acyl group.

48. The process of claim 46 wherein Pr is -C(O)-(C₁₋₄ alkyl).

49. The process of claim 46 wherein Pr is -C(O)Me.

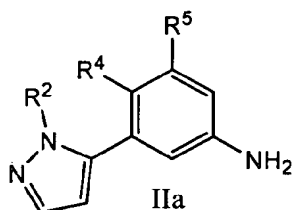
50. The process of claim 46 wherein said deprotecting agent is a base.

51. The process of claim 46 wherein said deprotecting agent comprises hydroxide.

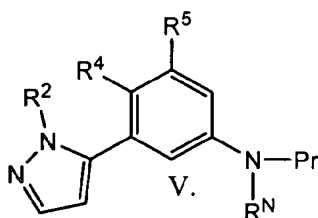
52. The process of claim 46 wherein said deprotecting agent comprises sodium hydroxide.

53. The process of claim 46 wherein said reacting with a deprotecting agent is carried out in an organic solvent.

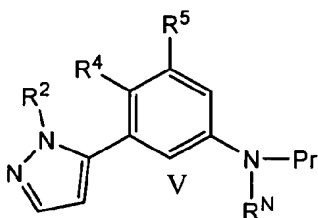
54. The process of claim 53 wherein said organic solvent comprises an alcohol.
55. The process of claim 53 wherein said organic solvent comprises methanol.
56. The process of claim 46 wherein said reacting with a deprotecting agent is carried out at reflux temperature.
57. The process of claim 46 wherein said reacting with a deprotecting agent results in formation of less than about 5 mole % of a compound of Formula IIa:



relative to the amount of compound of Formula II, and wherein said compound of Formula IV at the start of said reacting comprises a substantially undetectable amount of a compound of Formula V:



58. The process of claim 57 wherein said reacting with a deprotecting agent results in formation of less than about 3 mole % of a compound of Formula IIa.
59. The process of claim 46 wherein said compound of Formula IV is prepared by the process comprising reacting a compound of Formula V:



with a halogenating reagent for a time and under conditions suitable for forming said compound of Formula IV.

60. The process of claim 59 wherein said halogenating reagent is a brominating or chlorinating reagent.

61. The process of claim 59 wherein said halogenating reagent is a brominating reagent.

62. The process of claim 59 wherein said halogenating reagent comprises N-bromosuccinimide.

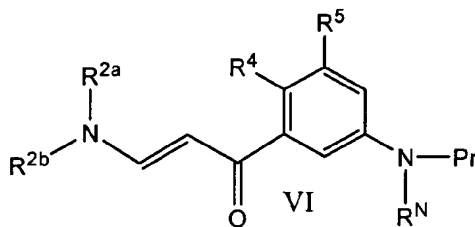
63. The process of claim 59 wherein said reacting with a halogenating reagent is carried out in an organic solvent.

64. The process of claim 59 wherein said organic solvent comprises an alcohol.

65. The process of claim 59 wherein said organic solvent comprises methanol.

66. The process of claim 59 wherein said reacting with a halogenating reagent is carried out at or below about room temperature.

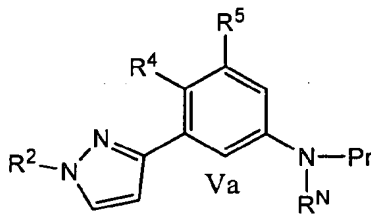
67. The process of claim 59 wherein said compound of Formula V is prepared by the process comprising reacting a compound of Formula VI:



wherein R^{2a} and R^{2b} are each, independently, C_{1-4} alkyl, with an alkylhydrazine having the formula NH_2NH-R^2 for a time and under conditions suitable for forming said compound of Formula V.

68. The process of claim 67 wherein R^2 is methyl.

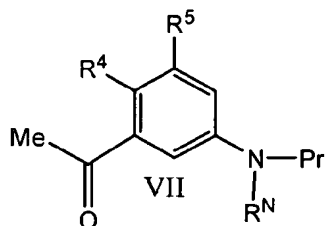
69. The process of claim 67 wherein said reacting with an alkyldiazine is carried out in the presence of an organic solvent.
70. The process of claim 69 wherein said organic solvent comprises an alcohol.
71. The process of claim 69 wherein said organic solvent comprises methanol.
72. The process of claim 67 wherein said reacting with an alkyldiazine is carried out in the presence of an acid.
73. The process of claim 72 wherein said acid comprises an inorganic acid.
74. The process of claim 72 wherein said acid comprises HCl.
75. The process of claim 67 wherein said compound of Formula VI is added to a solution containing said alkyldiazine and HCl.
76. The process of claim 67 wherein said reacting with an alkyldiazine further produces a compound of Formula Va:



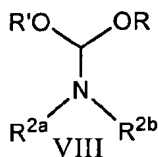
- wherein said compound of Formula Va is produced in a lesser amount than said compound of Formula V.
77. The process of claim 76 wherein the molar ratio of compound of Formula V to compound of Formula Va is greater than about 2.
78. The process of claim 76 wherein the molar ratio of compound of Formula V to compound of Formula Va is greater than about 5.

79. The process of claim 67 wherein said reacting with an alkyldiazine is carried out at a temperature of about -10 to about 30 °C.

80. The process of claim 67 wherein said compound of Formula VI is prepared by the processes comprising reacting a compound of Formula VII:



with an acetal of Formula VIII:



wherein R and R' are each, independently, C₁₋₆ alkyl, arylalkyl or alkylaryl, or R and R' together with the O atoms to which they are attached and the intervening CH group form a 5- or 6-membered heterocycloalkyl group, for a time and under conditions suitable for forming said compound of Formula VI.

81. The process of claim 80 wherein said R and R' are both C₁₋₄ alkyl.

82. The process of claim 80 wherein said R and R' are both methyl.

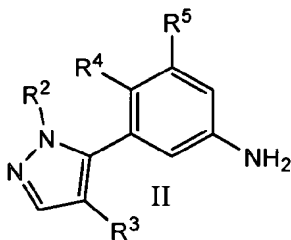
83. The process of claim 80 wherein said R^{2a} and R^{2b} are both methyl.

84. The process of claim 80 wherein said reacting with an acetal of Formula VIII is carried out in a solvent.

85. The process of claim 84 wherein said solvent comprises an alcohol.

86. The process of claim 84 wherein said solvent comprises ethanol.

87. The process of claim 80 wherein said reacting with an acetal of Formula VIII is carried out at about reflux temperature.
88. The process of claim 80 wherein said acetal is added to a mixture of said compound of Formula VII and solvent.
89. The process of claim 80 wherein said acetal is provided in molar excess relative to the amount of compound of Formula VII.
90. The process of claim 89 wherein the molar ratio of said acetal to said compound of Formula VII is about 1.5 to 3.
91. A process for preparing a compound of Formula II:



wherein:

R^2 is C_{1-4} alkyl;

R^3 is F, Cl, Br or I;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R^{11} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

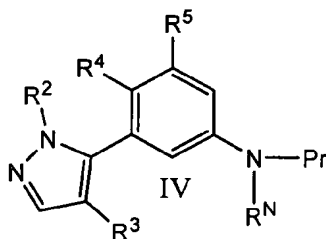
R^{12} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino,

R^{13} and R^{14} are each, independently, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C_{1-8} alkyl)carbonyl, (C_{1-8} haloalkyl)carbonyl, (C_{1-8} alkoxy)carbonyl, (C_{1-8} haloalkoxy)carbonyl, (C_{1-4} alkyl)sulfonyl, (C_{1-4} haloalkyl)sulfonyl or arylsulfonyl;

or R^{13} and R^{14} , together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group; and

wherein at least one of R^4 and R^5 is other than H;

comprising reacting a compound of Formula IV:



wherein:

Pr is an amino protecting group; and

R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;

with a base for a time and under conditions suitable for forming said compound of Formula II.

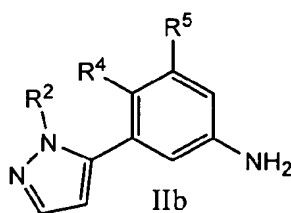
92. The process of claim 91 wherein Pr is an acyl group.

93. The process of claim 91 wherein Pr is $-C(O)-(C_{1-4}$ alkyl).

94. The process of claim 91 wherein Pr is $-C(O)Me$.

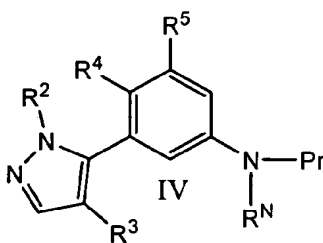
95. The process of claim 91 wherein said base is sodium hydroxide.

96. The process of claim 91 wherein said reacting is carried out in an organic solvent.
97. The process of claim 97 wherein said organic solvent comprises an alcohol.
98. The process of claim 97 wherein said organic solvent comprises methanol.
99. The process of claim 91 wherein the product of said reacting comprises less than about 5 mole % of a compound of Formula IIb:



relative to the amount of compound of Formula II.

100. The process of claim 99 wherein the product of said reacting comprises less than about 3 mole % of a compound of Formula IIb.
101. A process for the preparation of a compound of Formula IV:



wherein:

R^2 is C_{1-4} alkyl;

R^3 is F, Cl, Br or I;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6}

alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R¹¹ is, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R¹² is, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino,

R¹³ and R¹⁴ are each, independently, H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C₁₋₈ alkyl)carbonyl, (C₁₋₈ haloalkyl)carbonyl, (C₁₋₈ alkoxy)carbonyl, (C₁₋₈ haloalkoxy)carbonyl, (C₁₋₄ alkyl)sulfonyl, (C₁₋₄ haloalkyl)sulfonyl or arylsulfonyl;

or R¹³ and R¹⁴, together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

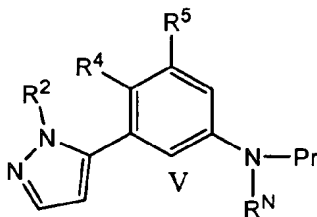
Pr is an amino protecting group; and

R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;

wherein at least one of R⁴ and R⁵ is other than H;

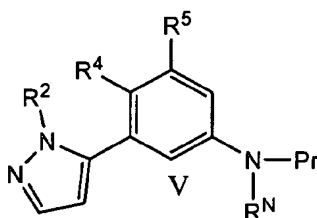
comprising reacting a compound of Formula V:



with a halogenating reagent for a time and under conditions suitable for forming said compound of Formula IV.

102. The process of claim 101 wherein said halogenating reagent is a brominating or chlorinating reagent.

103. The process of claim 102 wherein said halogenating reagent is a brominating reagent.
104. The process of claim 103 wherein said halogenating reagent comprises N-bromosuccinimide.
105. The process of claim 104 wherein said reacting is carried out in an organic solvent.
106. The process of claim 105 wherein said organic solvent comprises an alcohol.
107. The process of claim 106 wherein said organic solvent comprises methanol.
108. A process for preparing a compound of Formula V:



wherein:

R^2 is C_{1-4} alkyl;

R^3 is F, Cl, Br or I;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R^{11} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R^{12} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino,

R^{13} and R^{14} are each, independently, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C_{1-8} alkyl)carbonyl, (C_{1-8} haloalkyl)carbonyl, (C_{1-8} alkoxy)carbonyl, (C_{1-8} haloalkoxy)carbonyl, (C_{1-4} alkyl)sulfonyl, (C_{1-4} haloalkyl)sulfonyl or arylsulfonyl;

or R^{13} and R^{14} , together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

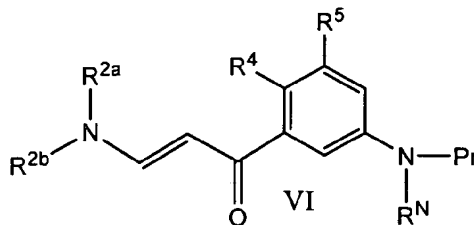
Pr is an amino protecting group; and

R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;

wherein at least one of R^4 and R^5 is other than H;

comprising reacting a compound of Formula VI:



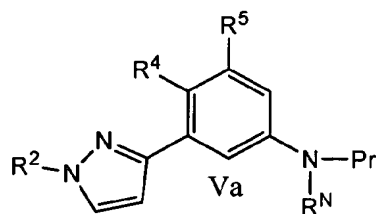
wherein R^{2a} and R^{2b} are each, independently, C_{1-4} alkyl, with an alkylhydrazine having the formula NH_2NH-R^2 for a time and under conditions suitable for forming said compound of Formula V.

109. The process of claim 108 wherein R^2 is methyl.

110. The process of claim 108 wherein said reacting is carried out in the presence of an organic solvent.

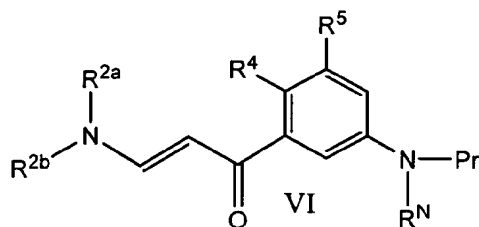
111. The process of claim 110 wherein said organic solvent comprises an alcohol.

112. The process of claim 110 wherein said organic solvent comprises methanol.
113. The process of claim 108 wherein said reacting is carried out in the presence of an acid.
114. The process of claim 113 wherein said acid comprises an inorganic acid.
115. The process of claim 113 wherein said acid comprises HCl.
116. The process of claim 108 wherein said compound of Formula VI is added to a solution containing said alkylhydrazine and HCl.
117. The process of claim 108 wherein said reacting further produces a compound of Formula Va:



wherein said compound of Formula Va is produced in a lesser amount than said compound of Formula V.

118. The process of claim 117 wherein the molar ratio of compound of Formula V to compound of Formula Va is greater than about 2.
119. The process of claim 117 wherein the molar ratio of compound of Formula V to compound of Formula Va is greater than about 5.
120. A process for preparing a compound of Formula VI:



wherein:

R^{2a} and R^{2b} are each, independently, C_{1-4} alkyl;

R^4 and R^5 are each, independently, H, halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, SR^{11} , SOR^{12} , SO_2R^{12} , COR^{12} , $COOR^{11}$, $OC(O)R^{12}$, $NR^{13}R^{14}$, or C_{3-7} cycloalkyl, wherein said C_{1-6} alkoxy group is optionally substituted with one or more C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-6} alkylamino, C_{2-8} dialkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} thioalkoxy, C_{1-4} alkylureido, amino, (C_{1-6} alkoxy)carbonyl, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R^{11} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R^{12} is, independently, H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino,

R^{13} and R^{14} are each, independently, H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heteroaryl, C_{3-7} cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C_{3-7} cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C_{1-8} alkyl)carbonyl, (C_{1-8} haloalkyl)carbonyl, (C_{1-8} alkoxy)carbonyl, (C_{1-8} haloalkoxy)carbonyl, (C_{1-4} alkyl)sulfonyl, (C_{1-4} haloalkyl)sulfonyl or arylsulfonyl;

or R^{13} and R^{14} , together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

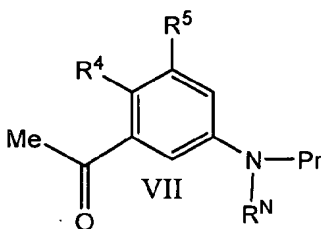
Pr is an amino protecting group; and

R^N is H;

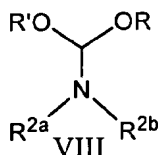
or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group;

wherein at least one of R^4 and R^5 is other than H;

comprising reacting a compound of Formula VII:



with an acetal of Formula VIII:



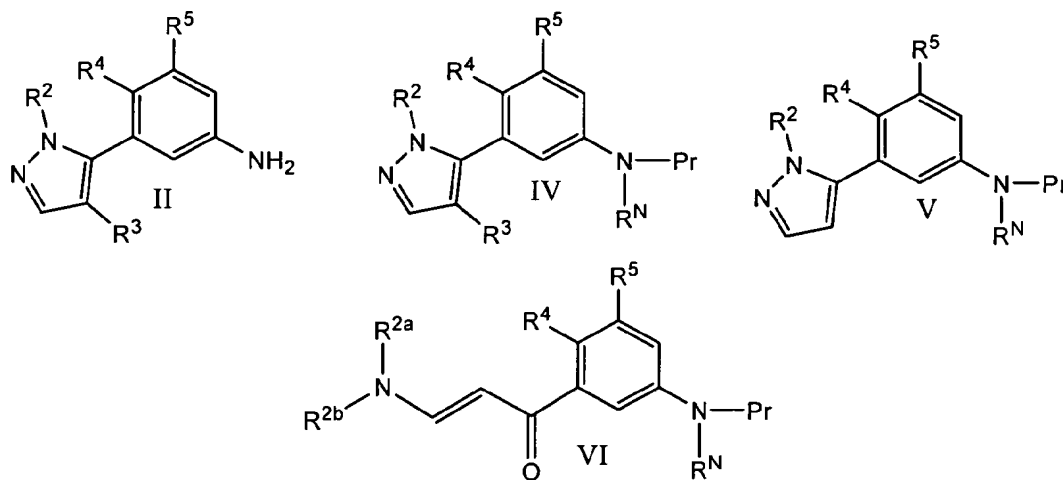
wherein R and R' are each, independently, C₁₋₆ alkyl, arylalkyl or alkylaryl, or R and R' together with the O atoms to which they are attached and the intervening CH group form a 5- or 6-membered heterocycloalkyl group; for a time and under conditions suitable for forming said compound of Formula VI.

121. The process of claim 120 wherein said R and R' are both C₁₋₄ alkyl.
122. The process of claim 120 wherein said R and R' are both methyl.
123. The process of claim 120 wherein said R^{2a} and R^{2b} are both methyl.
124. The process of claim 120 wherein said reacting with an acetal of Formula VIII is carried out in a solvent.
125. The process of claim 124 wherein said solvent comprises an alcohol.
126. The process of claim 124 wherein said solvent comprises ethanol.
127. The process of claim 120 wherein said reacting with an acetal of Formula VIII is carried out at about room temperature.
128. The process of claim 120 wherein said acetal is added to a mixture of said compound of Formula VII and solvent.

129. The process of claim 120 wherein said acetal is provided in molar excess relative to the amount of compound of Formula VII.

130. The process of claim 129 wherein the molar ratio of said acetal to said compound of Formula VII is about 1.5 to about 3.

131. A compound of Formula II, IV, V or VI:



wherein:

R² is C₁₋₄ alkyl;

R³ is F, Cl, Br or I;

R⁴ and R⁵ are each, independently, H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, SR¹¹, SOR¹², SO₂R¹², COR¹², COOR¹¹, OC(O)R¹², NR¹³R¹⁴, or C₃₋₇ cycloalkyl, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms;

R¹¹ is, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl or (5-7 membered heterocycloalkyl)alkyl;

R¹² is, independently, H, C₁₋₈ alkyl, C₁₋₈ haloalkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋

₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, amino, (C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino,

R¹³ and R¹⁴ are each, independently, H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl, heteroaryl, C₃₋₇ cycloalkyl, 5-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, (C₃₋₇ cycloalkyl)alkyl, (5-7 membered heterocycloalkyl)alkyl, (C₁₋₈ alkyl)carbonyl, (C₁₋₈ haloalkyl)carbonyl, (C₁₋₈ alkoxy)carbonyl, (C₁₋₈ haloalkoxy)carbonyl, (C₁₋₄ alkyl)sulfonyl, (C₁₋₄ haloalkyl)sulfonyl or arylsulfonyl;

or R¹³ and R¹⁴, together with the N atom to which they are attached form a 5-7 membered heterocycloalkyl group;

Pr is an amino protecting group;

R^N is H;

or Pr and R^N together with the N atom to which they are attached form a cyclic amino protecting group; and

R^{2a} and R^{2b} are each, independently, C₁₋₄ alkyl;

wherein at least one of R⁴ and R⁵ is other than H.

132. The compound of claim 131 wherein R² is methyl or ethyl.

133. The compound of claim 131 wherein R² is methyl.

134. The compound of claim 131 wherein R³ is Cl or Br.

135. The compound of claim 131 wherein R³ is Br.

136. The compound of claim 131 wherein R⁴ is other than H.

137. The compound of claim 131 wherein R⁴ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄

haloalkylsulfonyl, C₁₋₄ haloalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

138. The compound of claim 131 wherein R⁴ is C₁₋₆ alkoxy optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms.

139. The compound of claim 131 wherein R⁴ is C₁₋₆ alkoxy.

140. The compound of claim 131 wherein R⁴ is C₁₋₃ alkoxy.

141. The compound of claim 131 wherein R⁴ is methoxy or ethoxy.

142. The compound of claim 131 wherein R⁴ is methoxy.

143. The compound of claim 131 wherein R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

144. The compound of claim 131 wherein R⁵ is H.

145. The compound of claim 131 wherein R^{2a} and R^{2b} are both methyl.

146. The compound of claim 131 wherein Pr is -C(O)Me.

147. The compound of claim 131 wherein:

R³ is F, Cl, Br or I;

R⁴ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, wherein said C₁₋₆ alkoxy group is optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄

alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkoxy.

148. The compound of claim 131 wherein:

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy group optionally substituted with one or more C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₆ alkylamino, C₂₋₈ dialkylamino, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ thioalkoxy, C₁₋₄ alkylureido, amino, (C₁₋₆ alkoxy)carbonyl, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ halothioalkoxy, hydroxyl, nitro or phenyl optionally substituted with 1 to 5 halogen atoms; and

R⁵ is H.

149. The compound of claim 131 wherein:

R² is methyl or ethyl;

R³ is F, Cl, Br or I;

R⁴ is C₁₋₆ alkoxy; and

R⁵ is H.

150. The compound of claim 131 wherein:

R² is methyl;

R³ is Cl or Br;

R⁴ is methoxy; and

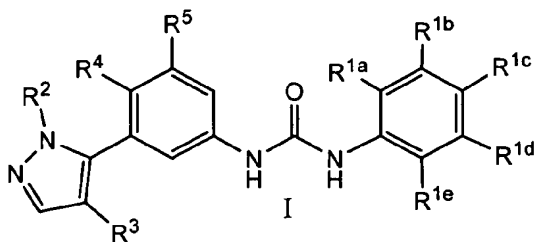
R⁵ is H.

151. The compound of claim 131 wherein said compound has Formula II.

152. The compound of claim 131 wherein said compound has Formula IV.
153. The compound of claim 131 wherein said compound has Formula V.
154. The compound of claim 131 wherein said compound has Formula VI.
155. The compound of claim 131 wherein said compound has Formula II and R^2 is methyl; R^3 is Cl or Br; R^4 is methoxy; and R^5 is H.
156. The compound of claim 131 wherein said compound has Formula IV and R^2 is methyl; R^3 is Br; R^4 is methoxy; R^5 is H; and Pr is $-C(O)Me$.
157. The compound of claim 131 wherein said compound has Formula IV and R^2 is methyl; R^3 is Cl; R^4 is methoxy; R^5 is H; and Pr is $-C(O)Me$.
158. The compound of claim 131 wherein said compound has Formula V and R^2 is methyl; R^4 is methoxy; R^5 is H; and Pr is $-C(O)Me$.
159. The compound of claim 131 wherein said compound has Formula VI and R^{2a} is methyl; R^{2b} is methyl; R^4 is methoxy; R^5 is H; and Pr is $-C(O)Me$.

ABSTRACT

The present invention is directed to processes for the preparation of substituted phenylpyrazole ureas of Formula I:



that are useful as 5-HT_{2A} serotonin receptor modulators for the treatment of disease.